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## Population structure and genetic heterogeneity in popular dog breeds in the UK

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### ABSTRACT

There is increasing concern that reproductive isolation related to breed specifications in dogs, while maintaining genetic differences among breeds, is likely to promote breed-specific genetic disorders. This study examined genetic diversity among 13 popular dog breed groups in the UK. Most breeds showed high levels of homozygosity when compared with crossbred animals. The Boxer and West Highland white terrier showed the lowest heterozygosity, while the Jack Russell terrier group (not a registered breed in the UK) had a level of heterozygosity comparable to crossbred dogs. Analysis of genetic distance between breeds showed significantly different inbreeding coefficients for pairwise comparisons among registered breeds, with the most divergent breeds being the Boxer and West Highland white terrier. The Rottweiler and Golden retriever showed the highest levels of inbreeding. The least distinct group contained crossbred dogs. The results show that the registered breeds are subject to a 'breed barrier' which promotes reduction in genetic diversity.

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### Introduction

The breed specifications for purebred/pedigree domestic dogs are defined by organisations which register and judge these animals, such as the Kennel Clubs of the UK<sup>2</sup> and America,<sup>3</sup> the Australian National Kennel Council<sup>4</sup> and the Kennel Union of Southern Africa,<sup>5</sup> as well as the umbrella body, the Fédération Cynologique Internationale (FCI).<sup>6</sup> Breeders tend to select stud animals which most closely comply with these specifications. Dogs can only be registered within a breed when both parents are also registered. Although new characteristics can be introduced into the breed, e.g. introducing the naturally bobbed tail from the Pembroke Welsh Corgi into the Boxer breed<sup>7</sup> (Haworth et al., 2001), several generations of mating back to registered members of the breed are required before animals containing the variant gene are registrable.

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<sup>2</sup> See: <http://www.thekennelclub.org.uk/>.

<sup>3</sup> See: <http://www.akc.org/>.

<sup>4</sup> See: <http://www.ankc.org.au/>.

<sup>5</sup> See: <http://www.kusa.co.za/>.

<sup>6</sup> See: <http://www.fci.be/>.

<sup>7</sup> See: <http://www.steynmere.com/>.

The reproductive isolation provided by this 'breed barrier' rule is likely to promote genetic differences among breeds and this has been demonstrated by studies of genetic admixture in domestic dogs in Finland (Koskinen, 2003) and the USA (Parker et al., 2004; Kanthaswamy et al., 2009). Many breeds of dogs in the UK have passed through genetic bottlenecks, largely due to line breeding to a small number of popular sires (Calboli et al., 2008). Selection for haplotypes around the genes for breed-specific traits (Pollinger et al., 2005) and high levels of inbreeding have resulted in the presence of genetic diseases characteristic of specific breeds (Asher et al., 2009; Summers et al., 2010; Leroy, 2011; Wade, 2011). This has led to interest in canine diseases as models for human disease and the drive to map genetic mutations for common conditions (Kirkness et al., 2003; Parker et al., 2009; Drögemüller et al., 2009, 2010; Pertica et al., 2010; Wang et al., 2010; Specht et al., 2011).

Within dog breeds in the USA, there appear to be at least four distinct sub-populations: Asian and African ancestry dogs (Oriental group), a group related to the Mastiff, a Herding dog group and a Hunting dog group (Parker et al., 2004). Some anomalies, including the inclusion of the German shepherd (GSH) in the Mastiff group, were found in the study by Parker et al. (2004). Breed specifications vary from country to country as different judges impose their preferences on the breed, e.g. the standard for height at the withers of a male Labrador retriever in the USA is greater than the standard

in the UK, South Africa and Australia, and a wider range of height is permitted. It might be expected that the same breed in different countries would gradually diverge genetically, although increasing use of artificial insemination in dog breeding and decreasing barriers to dog movement between countries may counteract this effect.

Indices of inbreeding and genetic admixture can be calculated from pedigrees, but these calculations do not account for differences in the initial levels of diversity within each breed. Furthermore, the assumption that founder animals within each breed are unrelated is unlikely to hold for any studbook, further confounding estimates of breed diversity derived from studbooks. The present study evaluated the molecular diversity within UK dog breeds based on neutral markers in the genome. Previous studies have been performed using purebred dogs as defined by registration with the American Kennel Club or other equivalent breed body (Koskinen, 2003; Parker et al., 2004; Sargan et al., 2007). In clinical practice, pedigrees are rarely known and breed is assigned by owner report or veterinarian observation. We examined the impact of this greater uncertainty on breed assignment and estimates of genetic variability.

## Materials and methods

### Samples

The study was approved by the University of Edinburgh Veterinary Ethical Review Committee (VERC 2011-99, 1 December 2008). Blood samples taken during veterinary clinical investigations were obtained from UK dogs through the Royal (Dick) School of Veterinary Studies, University of Edinburgh, Scotland, and Powell Torrance Diagnostic Services, Hertfordshire, England. Samples from Cavalier King Charles spaniels (CKCSs) were buccal swabs (Isohelix), taken with owner consent during an annual dog show. The breed of dog was taken as that stated by the owner or determined by a veterinarian during clinical examination. DNA was extracted from whole frozen blood samples following standard QiaGen DNeasy blood and tissue kit protocols. DNA was extracted from buccal swabs according to the manufacturer's instructions.

### Microsatellite genotyping and analysis

Amplification of 15 short tandem repeat (STR) loci, electrophoresis and genotyping were performed as described by Ogden et al. (2012). Genotype data were analysed for deviation from Hardy–Weinberg equilibrium (HWE) using GENEPOP (Raymond and Rousset, 1995).  $F$ -statistics were calculated using GENALEX (Peakall and Smouse, 2006) to estimate within-breed ( $F_{IS}$ ) and among-breed (pairwise  $F_{ST}$ ) inbreeding coefficients. STRUCTURE (Pritchard et al., 2000) was used to assign each dog to a breed category, assuming the admixture model, where animals can be characterised by a mixture of ancestral groups. All analyses were run with a 'burn-in' period of 100,000 and a sweep of 500,000 repetitions. Each set of parameters was repeated at least three times to assess whether the outcome was stable. The package SIMCO for the R statistical environment was used to obtain similarity coefficients.<sup>8</sup> Evidence of recent bottleneck events was investigated in each breed using BOTTLENECK (Piry et al., 1999), which assesses gene diversity (heterozygosity) excess relative to allelic diversity. A two-phase mutation model was implemented assuming 90% step-wise mutation. Analysis was based on the Wilcoxon sign-rank test and mode-shift distribution results.

## Results

### Relative genetic distances

Details of the number of samples and breed identifiers used in the analysis are given in Table 1. All loci were in HWE except for FH3377, where significant deviation ( $P < 0.01$ ) from HWE was observed; this was driven by heterozygote deficiency in Rottweilers and Yorkshire terriers, suggesting the existence of breed specific null alleles at this locus.

The relative genetic distances among breeds were examined by calculating mean pairwise  $F_{ST}$  values for each breed (Table 2); a

high  $F_{ST}$  value between two populations indicates that they are reproductively separate. All pairwise comparisons among true breeds showed significant  $F_{ST}$  values ( $F_{ST} > 0$ ,  $P = 0.01$ ), confirming the expected reduction in gene flow among breeds due to separation of breeding lines. The most divergent breeds were the Boxer and West Highland white terrier (mean  $F_{ST} = 0.26$  for each). The least distinct group was the crossbred group (mean  $F_{ST} = 0.10$ ), closely followed by the Jack Russell terrier group (mean  $F_{ST} = 0.11$ ).

### Genetic diversity

Genetic diversity was also examined using the level of inbreeding ( $F_{IS}$ ) and observed and expected heterozygosities ( $H_O$  and  $H_E$ , respectively). Positive  $F_{IS}$  values indicate inbreeding; high levels of heterozygosity indicate considerable outbreeding. The most diverse groups were crossbred dogs and Jack Russell terriers, closely followed by Yorkshire terriers, while the most inbred breeds were the Golden retriever and Rottweiler. The lowest heterozygosities were found in Boxers, GSDs and West Highland white terriers.

### Microsatellite genotyping

Genotype results for 15 microsatellite markers were loaded into STRUCTURE, specifying that the programme should find 2–20 subpopulations ( $K$ ). There was distinct differentiation between Kennel Club-registered breeds at  $K = 12$  (Fig. 1). There was no benefit to increasing  $K$  to  $>12$ , since all three runs at  $K \geq 12$  continued to detect 12 subpopulations representing the same 12 breeds, in which most individuals showed  $<10\%$  contribution from other subpopulations. The Jack Russell terrier group was as diverse as crossbred dogs and did not form a cohesive thirteenth group.

**Table 1**  
Breeds of dogs in the study.

Breed	Breed group <sup>a</sup>	Kennel club group <sup>b</sup>	<i>n</i>
Border collie	Hunting	Pastoral	20
Border terrier		Terrier	11
Boxer	Mastiff	Working	20
Cavalier King Charles spaniel	Hunting	Toy	25
English Springer spaniel		Gundog	25
German shepherd	Mastiff	Pastoral	20
Golden retriever	Hunting	Gundog	20
Jack Russell terrier		(Terrier)	23
Labrador retriever	Hunting/ Mastiff	Gundog	20
Rottweiler	Mastiff	Working	15
Staffordshire bull terrier		Terrier	20
West Highland white terrier	Hunting	Terrier	20
Yorkshire terrier		Toy	21
Cross breed			25
Unspecified cross			6
Border collie cross			1
Boxer cross			1
Cocker spaniel × Basset cross			1
Collie cross			7
German shepherd cross			1
German shepherd × Pointer cross			1
Labrador retriever cross			2
Rottweiler cross			1
Shih-Tzu × Bichon Frise cross			1
Spaniel cross			1
Staffordshire bull terrier cross			2
Total			285

<sup>a</sup> Breed group indicated if listed in Parker et al. (2004) where the four ancestral groups were Oriental, Mastiff, Hunting and Herding.

<sup>b</sup> Kennel Club group taken from <http://www.the-kennel-club.org.uk>. The Jack Russell terrier is not a registered breed but its near relative, the Parson Russell terrier, is in the terrier group.

<sup>8</sup> See: [http://rgm2.lab.nig.ac.jp/RCM2/func.php?rd\\_id=simco:simco.package](http://rgm2.lab.nig.ac.jp/RCM2/func.php?rd_id=simco:simco.package).

**Table 2**  
Estimated expected ( $H_E$ ) and observed ( $H_O$ ) heterozygosities, within-breed inbreeding co-efficient ( $F_{IS}$ ) and mean pairwise genetic differentiation ( $F_{ST}$ ) averaged across loci for the different breeds, together with available information on heritable disorders for each breed.

Breed	$H_E$	$H_O$	$F_{IS}$	Average $F_{ST}$ value <sup>a</sup>	Number of inherited disorders <sup>b</sup>	Cumulative severity range of inherited disorders <sup>c</sup>
Border collie	0.66	0.65	0.028	0.16	25	16–36
Border terrier	ND <sup>d</sup>	ND <sup>d</sup>	ND <sup>d</sup>	ND <sup>d</sup>	16	2–36
Boxer	0.51	0.51	–0.003	0.26	58	18–155
Cavalier King Charles spaniel	0.55	0.55	0.001	0.23	25	7–102
English Springer spaniel	0.68	0.68	0.000	0.16	53	62–138
German shepherd	0.54	0.52	0.041	0.23	69	35–123
Golden retriever	0.60	0.54	0.114	0.20	58	17–38
Jack Russell terrier <sup>e</sup>	0.76	0.75	0.016	0.11	ND	ND
Labrador retriever	0.68	0.66	0.028	0.15	51	29–79
Rottweiler	0.55	0.47	0.172	0.24	32	18–46
Staffordshire bull terrier	0.66	0.63	0.049	0.15	11	6–21
West Highland white terrier	0.52	0.49	0.058	0.26	35	0–75
Yorkshire terrier	0.66	0.73	–0.093	0.16	26	7–97
Cross breed	0.76	0.73	0.033	0.10	ND	ND

ND, Not determined.

<sup>a</sup> Average of pairwise comparisons with registered breeds.

<sup>b</sup> Data for UK dogs (Asher et al., 2009).

<sup>c</sup> Index calculated by Asher et al. (2009) based on assessment of prognosis, availability and success of treatment, complications and effects on behaviour of the inherited disorders.

<sup>d</sup> Border terriers were not included in the analysis of genetic diversity because of the low numbers. However they were included in the STRUCTURE analysis.

<sup>e</sup> Jack Russell terriers are not a registered breed in the UK and therefore were not included in the study of Asher et al. (2009).

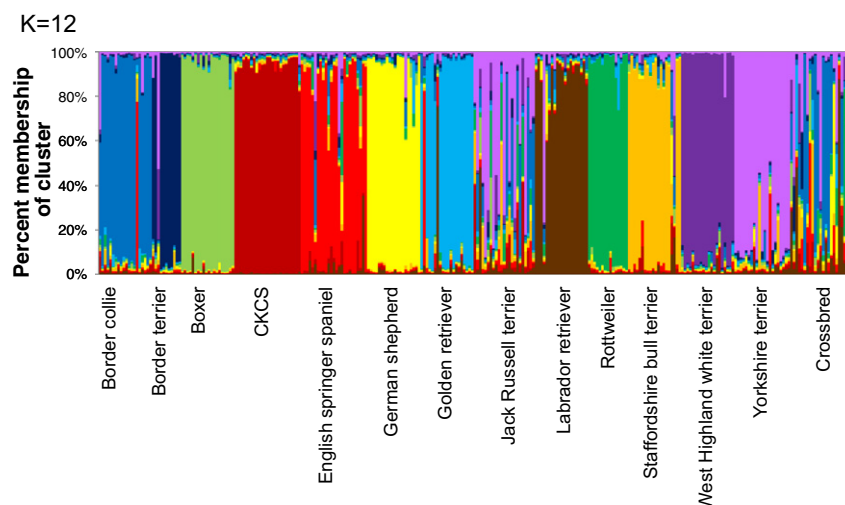
STRUCTURE analysis indicated that several animals had been assigned to the wrong breed. For example, one Golden retriever showed a genetic pattern common to Labrador retrievers, while several English Springer spaniels had <50% contribution of the dominant subgroup found for the other members of this breed. Boxers and Rottweilers were homogeneous, suggesting that they are rarely misclassified. CKCSs were also homogeneous, consistent with the collection of samples at a dog show, where all animals were pedigreed.

#### Level of heterozygosity and genetic divergence

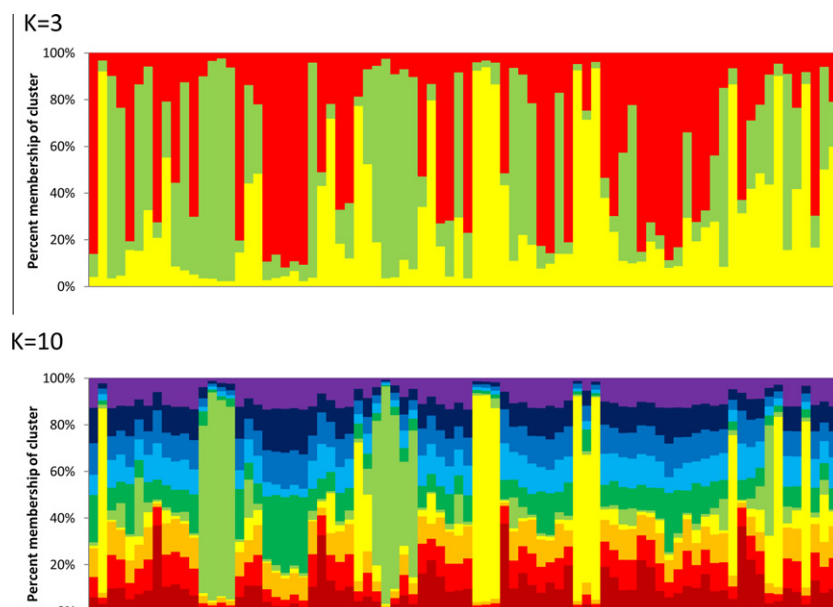
To assess within-breed indicators of diversity, the 13 groups, each with 15 or more animals, were compared by treating each as a separate population and running a series of standard population genetic analyses to compare levels of heterozygosity within breeds and to examine the relative level of genetic divergence among breeds. There was a broad and continuous distribution in

levels of expected heterozygosity ( $H_E$ ). Crossbred animals and Jack Russell terriers had  $H_E$  levels of 76%, whereas other breeds had  $H_E$  as low as 50% (Boxer, West Highland white terrier) (Table 2). All groups exhibited significant genetic distances from all other groups, except for crossbred dogs compared with Jack Russell terriers. Levels of within-breed inbreeding were high in the Rottweiler ( $F_{IS}$  = 0.172, mean =  $0.034 \pm 0.062$ ). This is in part due to the effects of the suspected null allele at locus 3377, but also reflects reduced heterozygosity across all loci.

Table 2 also shows the number of inherited diseases associated with the different breeds, taken from a previous study (Asher et al., 2009). There was no clear correlation between the level of heterozygosity and the incidence or severity of disease within the groups. For example, the English Springer spaniel with  $H_E$  of 0.67 is at risk for 53 genetic diseases, almost as many as the Boxer with a much lower  $H_E$  of 0.51 and risk for 58 diseases. The breeds with the highest inbreeding coefficients, the Rottweiler and Golden retriever, had 32 and 58 associated inherited disorders, respectively.



**Fig. 1.** Clustering assignment of 13 breeds of dog and a group of crossbred dogs. STRUCTURE was used to determine the admixture of each dog. Each breed is represented by 11–25 animals. A vertical line represents an individual dog. The line is divided into shaded segments indicating different genetic clusters and the length of each shaded segment indicates the estimated membership of that cluster. This analysis was run at a  $K$  value (number of genetic clusters) of 12; similar results were obtained for  $K$  values from 12 to 17. CKCS, Cavalier King Charles spaniel.



**Fig. 2.** Population structure of Cavalier King Charles spaniels. Microsatellite genotypes of 83 pedigree dogs were analysed with STRUCTURE at  $K$  values from 2 to 10. A clear indication of three subgroups was obtained at all  $K$  values above 2. The figure shows representative runs at  $K = 3$  and  $K = 10$ . At  $K = 3$ , one group of animals had >80% membership of the black cluster (yellow in the on-line coloured version), one had >60% membership of the light grey cluster (green in the on-line coloured version) and the third group had >50% membership of the white cluster (red in the on-line coloured version). No evidence of additional structure is seen with increasing  $K$ . At  $K = 10$  the first two groups maintained a high contribution from a single population (dark and mild grey (light green and yellow in the on-line coloured version)) but the third was more heterogeneous.

The results of BOTTLENECK analysis showed no evidence of bottlenecks in any of the breeds, with no significant excess of heterozygosity relative to allelic diversity observed in the Wilcoxon sign-rank test and mode-shift distribution data. Since this could be caused by the presence of subpopulations within a population (Wahlund, 1928), we analysed DNA from the CKCS, a breed which appeared to be homogeneous in the initial study. Samples from a further 58 animals (83 total) were subjected to STRUCTURE analysis at  $K$  values from 2 to 10. Three clear groups were seen (Fig. 2). The mean similarity coefficient at  $K = 3$  (four runs) was 0.98.

## Discussion

The group of animals used in this study represents a veterinary clinic population and the assignment to a breed was based on owner report and/or veterinarian assessment (other than CKCSs, which were pedigree animals at a dog show). Although previous studies have focused on purebred dogs with breed organisation registration, we felt it was important to assess the diversity in the range of dogs typically seen in veterinary practice. Understanding of clinical syndromes associated with a breed (for example mitral valve disease in CKCS) is dependent on recognising the breed and it is clear from our study that some breeds are consistently misclassified in practice. In contrast, Parker et al. (2004) analysed five purebred dogs per breed and showed a high degree of genetic similarity within breeds, with no evidence of the variability seen in our clinic population. Koskinen (2003) studied 50 dogs in five breeds and had 100% success in assignment of individuals to the breed specified and 100% exclusion success, with no evidence for genetic admixture within breeds. In our study, a similar result was achieved only for the CKCS, which were all pedigree animals, with low levels of admixture also seen in Boxer dogs and Rottweilers. The misclassification of other breeds limits genetic approaches in clinical practice and has implications for forensic analysis of evidence based on canine material.

In addition to the possibility of misclassification, our study shows that several breeds maintain a high degree of genetic diversity. In particular, the Jack Russell terrier group showed extensive admixture and low pairwise divergence from other breeds. This group is not a Kennel Club-registered breed in the UK, where a similar variety, the Parson Russell terrier, is registered.<sup>9</sup> UK breeders of Jack Russell terriers have indicated that they wish to maintain flexibility and focus on working characteristics by remaining outside the registration process.<sup>10</sup> In contrast, the Jack Russell breed is registered by the Kennel Union of Southern Africa.<sup>11</sup> The specifications for the Parson Russell terrier, a breed registered in the USA, are sufficiently broad that UK Jack Russell terriers would fall within the guidelines.<sup>12</sup> Therefore the Jack Russell/Parson Russell terrier group is diverse and the boundaries are not well defined. Some of the Jack Russell dogs in this study may have been bred as or from Parson Russells. This could account for the small subgroup with less genetic admixture. The Yorkshire terrier also showed elevated levels of observed heterozygosity and very low inbreeding.

When inter-breed ( $F_{ST}$ ) and intra-breed ( $H_E$ ) diversity measures were compared, a correlation of  $-0.99$  was observed, suggesting that higher heterozygosity is occurring in conjunction with a common suite of shared alleles among breeds, reducing breed divergence. In breeds displaying reduced heterozygosity, there appears to be a strong skew in allele frequencies towards extreme values (0 or 1), which is subsequently driving higher levels of breed divergence.

Using only animals with a high level of membership of a single population group, as demonstrated by the preliminary genetic analysis, we attempted to replicate the population assignment into four major groups of the previous study (Parker et al., 2004). The

<sup>9</sup> See: <http://www.the-kennel-club.org.uk/services/public/breeds/display.aspx?id=3175>.

<sup>10</sup> See: <http://www.jack-russell-terrier.co.uk>.

<sup>11</sup> See: <http://www.kusa.co.za/images/Documents/BSTerriers/Jack%20Russell%20Terrier.pdf>.

<sup>12</sup> See: [http://www.akc.org/breeds/parson\\_russell\\_terrier/index.cfm](http://www.akc.org/breeds/parson_russell_terrier/index.cfm).



STRUCTURE analysis gave multiple clustering solutions at  $K = 2$ –4. Members of each breed were always clustered together, but the inferred relationship between breeds varied. Therefore the similarity coefficients were low. This supports the observation of genetic distance between breeds, but does not reveal the relationships of the breeds. We had fewer breeds than the study by Parker et al. (2004) and did not have any animals from the Oriental or Herding groups. Four of the eight breeds used in this analysis (West Highland white terrier, CKCS, Golden retriever and Border collie) form a group with very similar memberships of the different populations in the previous data, while three other breeds (Rottweiler, GSH and Boxer) also show similar profiles. The Labrador retriever was intermediate between these two groups in the previous data. These findings are consistent with some of the clustering solutions shown by our analysis, but these results were not replicated through all STRUCTURE runs.

The lack of observed genetic bottlenecking in any breed is surprising given that the system of pedigree breeding would be expected to result in a situation where rare alleles were lost from each breed more rapidly relative to heterozygosity reduction. There are a number of possible explanations for this result. Despite a controlled breeding system, there may have been sufficient genetic augmentation of pedigrees, deliberate or accidental, to mitigate the reduction in allelic diversity. Alternatively, the presence of population structure within breeds due to multiple pedigree lines, which has been observed in the UK (Calboli et al., 2008), may counter a bottleneck signal by limiting breed heterozygosity through the Wahlund effect (Wahlund, 1928).

An analysis of 83 CKCSs (Fig. 2) confirmed the presence of subpopulations in this apparently homogeneous breed, presumably reflecting different ancestral subgroups. Although loci were widely observed to be in HWE across all breeds and significant heterozygote deficit at locus  $\times$  breed pairings was rare, elevated inbreeding at the level of the individual might be responsible for the failure to find evidence of bottlenecks.

We investigated the genetic diversity of UK dogs using a largely clinically defined population (i.e. animals that were assigned to a specific breed by the veterinarian or owner). Even though breed assignment was not based on pedigree registration for most animals, there was a high degree of uniformity and low heterozygosity in some breeds, including Boxers, Rottweilers and West Highland white terriers, as well as the CKCSs, which were collected at a show and therefore known to be pedigreed. This supports previous findings in UK dogs (Calboli et al., 2008).

These breeds are susceptible to a substantial number of heritable diseases, which is consistent with the level of inbreeding practised to maintain the breed standard (Asher et al., 2009). For example, almost all CKCSs have degenerative mitral valve disease by the age of 7 years and heritabilities of 0.3–0.6 have been shown for this condition (Lewis et al., 2011). CKCS also suffer from syringomyelia, for which an heritability of 0.37 has been calculated (Lewis et al., 2009). Boxers have a high predisposition to severe epilepsy (heritability 0.33; Nielsen et al., 2001) and West Highland terriers appear to be susceptible to idiopathic pulmonary fibrosis (Corcoran et al., 2011; Heikkilä et al., 2011). Inbreeding increases the level of homozygosity for detrimental alleles, for both monogenic and polygenic conditions. Dog groups with higher heterozygosities may also suffer from potentially genetic conditions. Jack Russell terriers are susceptible to monogenic and polygenic hereditary conditions, e.g. congenital recessive myasthenia gravis (Palmer, 1980; Wallace and Palmer, 1984) and hereditary ataxia (Wessmann et al., 2004), respectively. We did not find correlation between low heterozygosities or high inbreeding co-efficients and the number or severity of inherited conditions reported by Asher et al. (2009). This may reflect the assignment of mixed breed dogs to specific breeds in our analysis.

## Conclusions

Our results show that the breed barrier has operated in a clinic population of dogs, indicating that flow of genes is restricted. However there is also evidence of misclassification of dog breeds in this clinic population, which could influence larger studies of the genetic basis of disease in the general canine population. Some breeds (Boxer, West Highland white terrier) showed a low level of genetic diversity while the Jack Russell terrier group was as diverse as the crossbred dogs.

## Conflict of interest statement

None of the authors of this paper has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

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